to sickness. These two diseases, however, *are* ones against which individual protection may be achieved by available specific immunization procedures and both diseases are much more easily controlled by such immunization than by dealing with cases as they arise. Consequently, specific immunization of all Service personnel offers a specially important and desirable control measure.

It is not expected that specific immunization will *eliminate* diphtheria and scarlet fever from the Service. Scientific experience and expert opinion agree, however, that such a measure is the *most effective known weapon* of control. The introduction of the new R.C.A.F. immunization program is regarded as an important contribution to the Service.

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PROGNOSIS IN BILATERAL RENAL TUBERCULOSIS*

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RECENT statistics show that the incidence of tuberculosis in man is much less now than formerly. According to data published by the National Tuberculosis Association, clinical evidence of pulmonary tuberculosis is noted much less frequently than in former years. Henderson states that tuberculosis in the bones and joints has decreased to such an extent that some medical schools find it difficult to obtain a sufficient number of patients with such lesions for purposes of instruction. Most urologists agree that the incidence of renal tuberculosis has decreased definitely in the past two decades. There also has been a change in the clinical data which accompany the disease. The degree of involvement of the kidney and the bladder is less than in former years and the clinical evidence of its existence is often more obscure. This apparently is the result of reduction in etiological factors and of an increased resistance to tuberculous infection.

It would seem, on the contrary, that bilateral renal tuberculosis is reported more frequently in recent years than formerly. This is true particularly in reports from institutions for the treatment of pulmonary tuberculosis and from clinics where careful examinations of the urinary tract for evidence of tuberculosis are made. During the years 1910 to 1934 inclusive approximately 2,200 cases were observed at the Mayo Clinic in which a diagnosis was made of renal tuberculosis. Clinical evidence of bilateral involvement was present in 291 cases (13 per cent). Emmett and Kibler previously reported the prognosis in 87 of these cases in which nephrectomy was done on the more involved side, leaving 204 cases of bilateral renal tuberculosis in which no renal operation was done at the clinic.

The question may well be asked, what do we mean by bilateral renal tuberculosis? There is a decided difference among urologists as to the type and degree of evidence of disease deemed necessary to establish such a diagnosis. In the first place, there are the radicals who boldly state that all cases of renal tuberculosis are bilateral, at least at the time of onset. While this may be theoretically correct, there is insufficient pathological evidence available to substantiate such a statement and there is much clinical evidence to disprove it. It is generally believed that if the urine catheterized from the good kidney contains no pus cells, is negative for tubercle bacilli, and is negative on guinea pig inoculation, the kidney is normal and removal of the diseased kidney is permissible. Judging from the statistics of Emmett and Kibler, this particular group offers the best prognosis following nephrectomy. They found that the mortality rate five years after operation was 20 per cent and for ten years after operation, 34 per cent. One would be conservative in stating that bilateral renal tuberculosis would be very improbable in most of this group.

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Now comes another group, and this is where the controversy starts. In a series of cases observed at the clinic with proved tuberculosis in one kidney and with no microscopic evidence of infection in the urine from the good kidney, guinea pigs were inoculated with the apparently negative urine. We were surprised to note in how many cases the reports proved to be positive. After following many of the patients in this group who apparently recovered after nephrectomy, we concluded that in many cases the positive report from the guinea pig inoculation was the result of technical factors. In other words, that the tubercle bacilli were picked up by the ureteral catheter from the bladder or lower end of the ureter while in transit, or were present as the result of reflux into the ureter, which is often dilated in its distal portion. Too many of these patients recovered to permit the hypothesis of spontaneous recovery from active tuberculous involvement.

Next comes a group of cases in which three or more pus cells were found in the urine from the good kidney. Emmett and Kibler found that the five-year post-operative mortality in this group was 40 per cent, or twice as great as in cases with negative urine. Although the disease obviously was bilateral in many of these patients, in others it was not. When, in addition to more than three pus cells in the urine from the good kidney, the presence of tubercle bacilli was demonstrated, either by guinea pig inoculations or by staining the centrifuged specimen, the five-year mortality increased to more than 60 per cent. This still left a third of the patients who had definite evidence of bilateral disease at the time of operation who were alive five years or longer. Among this group were patients who, from subjective as well as objective evidence, apparently had recovered from their infection. It may be inferred from this that, (1) the kidney may recover occasionally from tuberculous infection; (2) positive evidence of disease in the good kidney as determined by inoculation of urine into guinea pigs sometimes is inaccurate and misleading; or (3) there is a definite group of individuals who get along pretty well with chronic renal tuberculosis. In our opinion the apparent recovery in most of these cases is explained by the last two inferences. It is quite evident that the demonstration of tubercle bacilli in the urine catheterized from the good kidney should not contraindicate the removal of the other kidney if it is extensively diseased. There may be other clinical factors, however, which may contraindicate it.

What are the indications for and against operation when there is definite evidence of active bilateral infection? It may be stated that unless there is a decided difference in the extent of the disease in the two kidneys surgical intervention is rarely indicated. In other words, the kidney which is removed should have evidence of extensive destruction of renal tissue or widespread involvement, while the involvement of the good kidney must be minimal. Even under such circumstances nephrectomy would not usually be indicated unless the diseased kidney was the cause of symptoms which a nephrectomy would remedy. It would be unreasonable to remove one kidney when the extent of the disease is equal in both kidneys. It is possible in rare cases that the lesion might be of equal extent in the initial stages and one kidney go on to more rapid destruction, giving rise to severe symptoms, while the disease remained stationary in the other, so that nephrectomy might then be considered.

It is taken for granted that operation is permissible only if the patient's general condition is satisfactory. The presence of tuberculosis in other tissues of the body, even if active, does not necessarily interfere with nephrectomy. In fact, as one of us (W.F.B.) previously observed, the concurrent chronic or previous tuberculosis in other tissues seems to increase resistance and gives a relatively good prognosis in many cases. Exceptions to this rule, however, are offered by active pulmonary complications, which would usually contraindicate surgery when both kidneys are involved. It would also be advisable to keep the patient under observation for a period of time, if the bilateral disease is of recent origin, in order to determine its localization and to improve the patient's resistance.

Although surgical treatment is not indicated in most cases with definite evidence of bilateral renal tuberculosis, in selected cases removal of a kidney with extensive involvement may be followed by great relief of symptoms and improvement in the general condition. In most cases with bilateral renal tuberculosis, however, there is not a great difference in the degree and extent of renal disease, and other complications usually are present, so that surgical treatment is not possible. The clinical course of these patients must necessarily depend on their power

of resistance and on therapeutic measures which will aid it. We have reviewed the clinical data and course of 204 patients with definitely proved bilateral renal tuberculosis observed at the clinic in whom surgical treatment seemed inadvisable.

Sex and age.—Only 39 patients, or 19 per cent, of the group were women. The preponderance of male patients is greater with bilateral renal involvement than with unilateral disease, the rate being four to one, as compared with two to one. Apparently there is not much difference in the distribution of these cases according to age from that observed with unilateral involvement. It was found that 58.8 per cent of the patients were in the fourth and fifth decades. The youngest patient was an infant twenty-eight months old, who developed miliary tuberculosis and died a few days after registration at the clinic. The oldest patient was sixty-three years of age, who lived two years after his examination. The age-distribution and chronicity of the disease make these patients a social as well as a medical problem. The majority of the patients are too ill to work and the disease strikes when their earning capacity should be at its height.

The symptoms did not differ very much from those observed with unilateral tuberculosis, except that they were more severe. A history of a period of dysuria and frequent micturition many years before, with recovery and then a recent recurrence of symptoms, was elicited in 34 cases (16.6 per cent). This corresponded to the period of infection and occlusion of one kidney with recent infection in the other. In fact, with a clear-cut history of this kind the diagnosis of bilateral involvement usually can be inferred.

Roentgenographic studies showed areas of renal calcification present in 19.6 per cent of our cases. The degree of calcification was variable, but on the whole more massive than that seen in unilateral cases. Forty cases of occluded renal tuberculosis were found in this series.

Cystoscopic examination usually reveals much more involvement of the bladder, with deformity and ulceration, than is observed with unilateral renal tuberculosis. In many cases a necrotic surface covering the entire bladder mucosa is observed. The patient usually is so intolerant that general or spinal anæsthesia is necessary. In early cases of bilateral involvement, however, the bladder may be almost normal on cystoscopic examination. The presence of many pus cells together with bacteria other than tubercle bacilli was noted in the catheterized specimen from the "good" kidney in several cases. Inoculation of guinea pigs with this urine and examination of the sediment for tubercle bacilli were reported as negative. It is very evident that the renal infection was caused by a non-tuberculous pyelonephritis present in the so-called "good" kidney. It also is evident that the presence of pus cells alone in the urine from the good kidney does not necessarily indicate the presence of tuberculosis.

In some cases of bilateral tuberculosis in which infection is limited the catheterized specimen of urine from either kidney may contain no pus cells whatever, but when the examination is repeated a variable number of pus cells may be present. Although there may be no pus cells in the catheterized urine in a case of this kind guinea pig inoculations may prove to be positive. As Thomas has emphasized, in some of these cases bilateral retrograde pyelography will be necessary to recognize the lesion. The urographic deformity may be so slight in these cases that it will be missed completely in the excretory urogram. A considerable degree of ureterectasis may often be noted, particularly in the lower third of the ureter from the good kidney. This can best be explained by an ascending ureteritis which is not necessarily of a tuberculous nature. It is easy to understand how bacilli washed up from the bladder can be picked up from the dilated ureter by the ureteral catheter.

Complications.—Bugbee and Thomas remind us that renal tuberculosis is a local manifestation of a constitutional disease. Evidence of pulmonary tuberculosis was noted in 77 of our cases, or 37.7 per cent. According to x-ray evidence, the pulmonary lesion was regarded as active in 47 cases and healed in 30 cases. Tuberculous involvement of the genitalia was noted in 91 cases, or 44.6 per cent, which is no higher than in cases of unilateral renal tuberculosis. Tuberculous bone lesions were found in 31 cases, or 15.2 per cent, of the cases of bilateral renal tuberculosis, which corresponds to 11 per cent reported with unilateral renal lesions.

Among the complications of unusual interest may be mentioned lupus vulgaris, which was discovered in three patients. In one of these patients, a man aged 28 years, the disease had existed for sixteen years and it was the only extrarenal complication at the time of examina-

tion. Tuberculosis was observed in one patient with a solitary kidney. Agenesis was inferred from absence of any evidence of a ureteral orifice in the corresponding half of the bladder on numerous cystoscopic examinations and was corroborated by subsequent surgical exploration. In two male patients vesicorectal fistulæ were found. Although it has been observed rather rarely in the past fifteen years numerous cases of cervical adenitis were noted in the earlier histories.

Renal function.—A slight reduction in function usually is noted in the early stages of unilateral renal tuberculosis. It is of interest, however, that in spite of apparently advanced involvement of both kidneys, the combined renal function often is normal or only slightly reduced. This observation is in keeping with that noted in other types of chronic bilateral renal infection. Even in cases of occlusion of one kidney and extensive infection in the other kidney there may be little or no rise in the blood urea. It is often surprising how little subjective evidence of renal insufficiency is observed in cases with greatly reduced renal function, as sometimes occurs in the terminal stages of bilateral renal tuberculosis. The urea content of the blood was determined in 117 cases with bilateral tuberculosis and a value under 45 mg. per 100 c.c. of blood was noted in 80 patients, or 68 per cent. The urea content of the blood was less than 45 mg. per 100 c.c. in 31 of the 40 cases of bilateral renal tuberculosis with occlusion of one kidney.

Hypertension.—It has been shown in a previous communication by Walters, Hammer and one of us (W.F.B.) that the incidence of hypertension with unilateral renal tuberculosis is less than that observed among average persons. The question arose as to what influence *bilateral* renal tuberculosis would have on blood pressure. A systolic blood pressure of 145 mm. or more was noted in 19.5 per cent of the 180 cases in which the blood pressure was determined. This is but slightly higher than its incidence with unilateral disease. Included in this series are 40 cases of functionless, occluded renal tuberculosis in one kidney with chronic tuberculosis in the other. Hypertension was present in 7 of these cases, or 17.5 per cent. It is evident that the changes in the renal tissues secondary to tuberculosis, even when bilateral, do not affect the vascular supply with secretion of pressor substances, as occurs with atrophic pyelonephritis.

PROGNOSIS

The subsequent clinical course was traced in 167 of 204 cases with definite clinical evidence of bilateral renal tuberculosis observed at the clinic. The survival rates are calculated from the time of onset of urinary symptoms. Although exact data as to the cause of death were not available in many of these cases, judging from the reports received from the attending physician and relatives, most of the patients traced died, directly or indirectly, from some form of tuberculosis.

One hundred and twenty patients, or 71.9 per cent, of the patients traced, survived three years or more and 86 patients, or 58.1 per cent, survived five years or more. Thirty-five patients, or 26.3 per cent, were found to be living ten years, and 14 patients, or 15.9 per cent, fifteen years. It is of interest that the general condition of most of the patients alive ten and fifteen years after examination was better than might be expected and of some was quite normal. Frequent urination was usually present to a variable degree. It was believed (Wildbolz) for many years that the survival of patients with untreated unilateral renal tuberculosis over a period of ten years or more was exceptional, and fifteen years was very rare. Judging from the number of our patients with bilateral tuberculosis who survived ten years, and even fifteen years, our concepts concerning life expectancy with non-surgical renal tuberculosis demand revision. In fact, if the advisability of operation in a given case is debatable, the possibility of long survival without surgical interference must be considered.

The prognosis in cases of bilateral renal infection of equal degree is distinctly worse than in cases with infection predominant in one kidney. Among the 63 cases with equilateral infection 42 patients, or 66.6 per cent, died within two years and only 7 were alive five years or more. The influence of active pulmonary tuberculosis complicating bilateral renal tuberculosis is shown by the fact that of 47 such cases 33, or 70 per cent, were dead in less than three years and only one patient was alive after seven years. The prognosis with occluded tuberculosis in one kidney and active tuberculosis in the other was definitely better than in the average case with bilateral disease. Of 40 cases with occluded renal tuberculosis only 15 died within three years after the onset of disease in the second

kidney and 17 lived from six to twenty-two years.

In reviewing the cases in which there seemed to be more resistance to the disease it is difficult to find any outstanding feature that is common to all. The care of the patient after leaving the clinic was at best inadequate. A small number of patients had sporadic sanitarium care, and they seemed to do well. However, in the main they were at the sanitariums too short a time and, when they left, they immediately engaged in the rigours of earning a livelihood. It would seem probable that with supervised rest, good diet, and heliotherapy, the survival rate of these persons would increase.

What has happened to the renal infection in those patients who are alive ten years or more? In a few cases it is possible that spontaneous recovery has taken place in one kidney at least. In some cases one kidney has become occluded. In most cases the tuberculous infection persists, although dormant most of the time. Although periods of increased activity in limited renal areas probably occur at intervals, the degree of resistance is such that the infection is soon controlled. The patient usually becomes so accustomed to areas of infection in the bladder that their presence does not bother him much. Evidence of renal insufficiency is slow in developing, since the disease involves the medullary and interstitial elements of the kidney rather than the glomeruli. Although the general physical condition is satisfactory in many cases with chronic bilateral tuberculous infection, complete healing occurs only in exceptional cases.

Three patients in our series lived twenty years or more and their clinical course warrants detailed comment. Two of these patients are still living, the other, after living twenty years, "died of a tuberculous process", according to the attending physician.

CASE 1

A woman, aged 30 years, was first examined at the clinic in 1915. Examination of the urine collected from each kidney revealed the presence of pus cells grade 1 (on a basis of 1 to 4), and bacillus of tuberculosis in both kidneys, as proved by acid-fast stains of the sediment of the urine and by guinea-pig inoculations. The patient was seen again in 1919 and, although the urine contained a few pus cells, acid-fast stains and guinea-pig inoculations were negative. The renal function as determined by phenolsulphonphthalein in the catheterized specimens of renal urine was apparently slightly decreased on both sides. She returned in 1923 and at that time cystoscopic examination and a study of the separated specimens of urine were negative. The renal function was normal. In 1938 she returned because of intermittent attacks of urgency and frequency, apparently caused by a mild, apparently non-tuberculous infection. Smears made from sediment of the urine were negative for acid-fast bacilli and the guinea-pig inoculations of the catheterized renal specimens of urine were also negative. A plain roentgenogram of the urinary tract, however, showed small, irregular areas of calcification over the left renal area which were very suggestive of tuberculous calcification, although calculus could not be excluded. The excretory urogram showed no deformity in the pelvis, calices or ureter. This patient has had excellent care, including diet, rest and heliotherapy. When examined recently she was in good general health, complained of no urinary symptoms, and examination of the urine was negative.

CASE 2

A man, aged 22 years, came to the clinic in 1920, complaining of gross hæmaturia and marked frequency of three years' duration. This patient had lupus vulgaris for 16 years. Urological examination showed a functionless, occluded left kidney; the urine catheterized from the right kidney contained pus, grade 2, and an acid-fast stain was positive for tubercle bacilli. He had no other evidence of systemic tuberculosis. He returned in 1936 with symptoms of dysuria and frequent micturition. On physical examination tuberculosis of the right knee was found, which required surgical intervention. A plain roentgenogram made at this time showed calcification along the course of the left ureter which was not present on previous examination. The urea content of the blood was 50 mg. per 100 c.c. The patient returned again in 1938 with a history of recent hæmaturia and pain in the left testicle. The right testicle was undescended. A left orchidectomy was performed and caseous tuberculosis of the testicle, with involvement of the epididymis, was found. He returned again in 1939 complaining of frequency and a moderate degree of urinary obstruction. The urine contained pus, grade 4, and stains for tubercle bacilli and guinea-pig inoculations were positive. A stricture of the anterior urethra was found. Evidence of renal insufficiency was indicated by the urea content of the blood, which was 78 mg. per 100 c.c.

This case brings up one other interesting point besides the long survival and long history of lupus. The left testicle, which had been normal on all previous examinations during eight years, was found to harbour tuberculosis, while the undescended right testicle gave no clinical evidence of being involved at any time. Since his last examination this patient had enjoyed relatively good health in spite of evidence of renal insufficiency.

CASE 3

A man, aged 23 years, came to the clinic in 1912 complaining of marked frequency and gross hæmaturia intermittently for the preceding five years. A diagnosis of bilateral renal tuberculosis had been made elsewhere. Before his visit here in 1912 he had had a left orchidectomy for tuberculosis of the testicle in 1907 and a cystostomy for severe dysuria in 1911. At his first visit to the clinic examination of the voided urine revealed pus, grade 2; cystoscopic examination showed diffuse cystitis, and guinea pigs inoculated with the urine from the right kidney gave a positive test for tuberculosis. A ureteral orifice could not be found on the left side and no elevation of the trigone was noted on cystoscopic examination. Surgical exploration of the left renal area revealed "no kidney tissue". The patient returned in 1926 and urine from the bladder and right kidney gave a positive guinea-pig test. A plain roentgenogram made at this time showed "multiple shadows in the lower pole of the

right kidney which probably represent walled-off caseous areas''. This patient died ''of tuberculosis'' in 1928, after living 21 years with renal tuberculosis in a solitary kidney.

SUMMARY AND CONCLUSIONS

The incidence of renal tuberculosis in recent years is definitely less than formerly.

There is a difference of opinion as to the clinical data necessary to establish the diagnosis of renal tuberculosis in doubtful cases. The presence of tubercle bacilli in the catheterized renal urine, as determined by positive inoculation of guinea pigs, is not sufficient. There also should be at least 3 to 10 pus cells present, and in some cases positive urographic deformity, in order to make the diagnosis certain.

A diagnosis of bilateral renal tuberculosis was made in 291 cases, or 13 per cent, of 2,200 cases of renal tuberculosis observed at the Mayo Clinic during the years 1910 to 1934. Eighty-seven of these patients were subjected to nephrectomy, leaving 204 cases of bilateral tuberculosis for which operation was not done.

Nephrectomy with bilateral renal tuberculosis is indicated only when there is decided differences in the extent of the lesion in the two kidneys. Nephrectomy would not usually be indicated unless the diseased kidney was the cause of symptoms requiring relief.

The incidence of unilateral renal tuberculosis in male patients is twice that in female patients. The incidence of bilateral renal disease in the male is twice as great as with unilateral disease.

A clear-cut history of a period of dysuria and frequent micturition many years ago and then a recent recurrence of symptoms is frequently elicited and is typical of bilateral involvement.

Cystoscopic examination usually reveals greater degree of involvement of the bladder than with unilateral disease.

The occurrence of previous tuberculosis in other tissues often seems to increase the patient's resistance and may be accompanied by a relatively good prognosis.

In spite of advanced bilateral involvement of both kidneys, the combined renal function often is normal or only slightly reduced. Little subjective evidence of renal insufficiency was observed in many cases in which the renal function was greatly reduced.

The incidence of hypertension with bilateral renal tuberculosis is very little higher than the average incidence of hypertension observed in adults.

The subsequent clinical course was traced in 167 cases with definite clinical evidence of bilateral renal tuberculosis.

The survival of patients traced after three years or more was 72 per cent; after five years or more, 58 per cent; after ten years or more, 26 per cent, and after fifteen years, 16 per cent. Most of the patients alive ten or fifteen years after examination were reported as being in a fairly normal condition, except for a variable degree of frequent urination.

Therapeutic measures, such as sanitarium treatment or the advantages of rest, diet and sunshine, undoubtedly are factors in aiding longevity.

Our previous concepts concerning life expectancy with non-surgical renal tuberculosis demand radical revision. Unless the indications for nephrectomy are quite definite in a case with bilateral disease, it would be well to give nature a chance.

U.S. ARMY TYPHOID VACCINE.—In the last year the output was increased more than eight times. A total of 33,500,000 c.c., the equivalent of 8,500 gallons of typhoid vaccine, were made. This represents a saving to the government of $1,540,000 over the cost of purchase. Typhoid vaccine is being made by the Army with a culture from the body of a typhoid fever carrier in the Panama Canal Zone, who is kept under constant supervision by Army doctors. The original typhoid culture came from an English soldier who died in the Boer War, but recent investigation showed this strain had lost its potency. The cultures are preserved in glass tubes by a special process at a temperature of 108 degrees below zero and sealing in a partial vacuum. These tubes of cultures can be preserved for long periods.—From the *J. Am. M. Ass.*, 1941, **117**: 538.